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Physiology and Medicine at High Altitude: The Exposure and the Stress

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ABSTRACT

Increase in altitude causes decrease in atmospheric barometric pressure that results in decrease of inspired partial pressure of oxygen, a source for stress and pose a challenge to climbers/trekkers or persons posted on high altitude areas. This review discusses about the high altitude sickness, their incidence rates, pathophysiology and the classic model of acclimatisation, which explains about how oxygen requirement in extreme environment is achieved by complex interplay among pulmonary, hematological and cardiovascular processes. The acute high altitude illness (AHAI) is basically composed of two syndromes: cerebral and pulmonary that can afflict un-acclimatised climbers/trekkers. The cerebral syndrome includes acute mountain sickness (AMS) and high altitude cerebral oedema (HACO) and pulmonary syndrome typically refers to high altitude pulmonary oedema (HAPO). The core physiological purpose, according to the classic model is centered upon the optimisation of increased delivery of oxygen to the cells through a coherent response involving increased ventilation, cardiac output and hemoglobin concentration with aim to increase the oxygen flux across the oxygen cascade, which will help in preventing the development of majority of high altitude illness.

Keywords: High altitude; Oxygen delivery; Hypoxic response; Cardiovascular optimisation; Cardiac output

1. INTRODUCTION

As the altitude increases, the atmospheric barometric pressure decreases and there occurs a concomitant fall in the inspired partial pressure of oxygen (PiO_2), even though the relative percentage of oxygen (FiO_2) remains unaltered at 20.9 per cent. This lowered PiO_2 creates the foundational stress of hypobaric hypoxia. While, this was first recognised in 1820 by a Russian climber Joseph Hamel who advised the use of supplemental oxygen on ascents of Mt. Blanc[1], it was sometimes in the mid-nineteenth century that, Bert first showed the association between hypobaria triggered lowering of PiO_2 and high altitude illness[2].

This relationship is best captured by the gas-law equation:

$$PV = nRT$$

where P = pressure, V = volume, n = number of gas molecules, R = universal gas constant, and T = absolute temperature.

Since, the partial pressure of a gas, $P = Fi \times B$, at sea level given a B of 760 mmHg (P_B), the partial pressure of inspired O_2 becomes = 20.9 x 760 =159 mm Hg. This fall is most dramatic at 5,486 meters, which is the upper level of functional acclimatisation where a PB of = 395 mm Hg yields a Pi O_2 of 82 mmHg (20.9 x 395), which is nearly half that at sea level. Even at 3000 m, the height of Leh, the barometric pressure (P_B) and inspired PO_2 (PiO_2) are only 70 per cent of the sea level values. On the summit of Mt. Everest, at 8848 m, the PiO_2 is less than 30 per cent of its sea level value. These values signify the stress and challenge to the physiology at high altitude.

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2. THE ADAPTATION

Taken suddenly to the top of Mt. Everest (8848 m), a person would lose consciousness in less than 3 min[3]. Taken slowly the same person remains alive and functional. In fact the lowest recorded P_AO_2 in a healthy individual at 8400 m on Everest by the Caudwell Xtreme Everest expedition was 19 mmHg (2.55 KPa). The stark contrast between the two scenarios is accounted for by the adaptive process called acclimatisation that tends to increase the oxygen delivery (DO_2) to the tissues.

3. THE CLASSIC MODEL

The classic model holds that this increase in DO_2 is affected by an optimisation between: (i) Pulmonary (ii) haematological and, (iii) cardiovascular processes. Pulmonary process optimisation is the first response to hypobaric hypoxia: hyperventilation is triggered by a combination of stimulation of peripheral chemoreceptor and inhibition of the central chemoreceptors that leads to an increased respiratory rate and depth. This hypoxic ventilator response (HVR) triggers in within a few hours of exposure to hypobaric hypoxia. This HVR tends to restore the falling oxygen gradient across the

oxygen cascade by raising the alveolar ventilation and alveolar $PO_{2\,(PAO2)}$ in its wake. Since the P_AO_2 is a function of the alveolar gas equation: $P_AO_2 = PiO_{2--}\ (P_ACO_2)/R$, so as the HVR raises the rate and depth of respiration, an increasing CO_2 washout leads to a decline in P_ACO_2 and a corresponding rise in P_AO_2. This rise in P_AO_2 tends to increase the partial pressure of O_2 all the way from the alveolus to the mitochondria and hence, improving the O_2 gradients across the cascade.

Along with HVR, the second component of the pulmonary optimisation involves hypoxic pulmonary vasoconstriction (HPV) and increased pulmonary artery pressures (PAP). This process of HPV serves to increase the flow and re-distribute the blood supply towards alveoli with higher oxygen content (P_AO_2) thereby improving the ventilation perfusion (V/Q) ratio. This increase in alveolar ventilation generates respiratory alkalosis due to CO_2 washout, which is metabolically compensated by the kidneys through increased urinary HCO_3^- loss. Serum HCO_3^- values of 10.8 meq/L, P_ACO_2 of 13.3 mmHg and a pH of 7.53 were recorded in healthy climbers at 8400 m on Mt. Everest by the Caudwell Xtreme Everest Expedition.

4. HAEMATOLOGICAL OPTIMISATION PROCESS

Oxygen carriage in blood is primarily a function of following interactive variables:

$CaO_2 = (SaO_2$ x 1.34 Haemoglobin, Hb) + (0.003 x $P_AO_2)$

where 1.34 = Huffners constant (ml of O_2 carried by 1 gm of Hb), and CaO_2 is O_2 carrying capacity of blood. The oxygen content of the blood within the frame of this CaO_2 equation is increased by a combination of an increase in haemoglobin and a decrease in its affinity for O_2 (i.e. a leftward shift of the OD curve). Hb rises during acclimatisation through a two-step process: Acutely, as a consequence of diuresis induced contraction of plasma volume by 30 per cent engendering haemo-concentration[4] and within 2-3 h of hypoxic exposure as a consequence of increased erythropoietin (EPO) release by the kidneys. However this hemo concentration induced increase in CaO_2 also engenders a paradoxical disruption of microcirculatory blood flow, possibly by hyper viscosity effect that may decrease the tissue DO_2. This paradox has been demonstrated by Martin et al at an altitude of 4900 m[5].

While the O_2 binding and carrying capacity of Hb raises, the affinity of O_2 for Hb determined by the oxygen –dissociation curve (ODC), decreases thereby increasing the ease of O_2 release from Hb.

Though the initial hyperventilation triggered respiratory alkalosis shifts the ODC leftwards, decreasing O_2 release from Hb, over a period of 7 days or so an increased renal synthesis of 2,3-Di-phosphoglycerate (2,3- DPG) forces a right wards correction.

5. CARDIOVASCULAR OPTIMISATION PROCESS

If the prime purpose of acclimatisation is to increase the DO_2 to the tissues, then DO_2 can be constructed as product of the oxygen carrying capacity of blood and cardiac output (Q). Thus $DO_2 = CaO_2\ x\ Q$. Cardiac output (Q) is itself a product of: Heart rate (HR) and stroke volume (SV). Thus $Q = HR\ x\ SV$. With exposure to altitude, while Q reduces for the initial few weeks, it returns to sea level values after several weeks chiefly on the account of raised HR, despite stroke volume SV remaining low[5].

6. CELLULAR LEVEL OPTIMISATION

These remain the least understood. While increased mitochondrial and capillary densities in the muscles were initially thought to play a major role in acclimatisation, recent work by Martin[5], *et al.* and Caudewell Xtreme Everest Expedition have shown that it was in fact altitude induced sarcopenia which produced a relative increase in capillary density. There was no true neo-vascularisation. Martin[5], *et al.* demonstrated a 30 per cent reduction in mitochondrial density in their muscle biopsy samples.

Hypoxia inducible Factor-I (HIF-I) is the master transcription factor that triggers the transcriptional activation of a host of hypoxia responsive genes ranging from (i) erythropoietin (EPO), (ii) glycolytic enzymes such as aldolase–A (ALDA), Enolase-I (ENO-I), Lactic dehydrogenase–A (LDH-A), phosphofructokinase–L (PKK-L) & Haemeoxygenase, (iii) inducible Nitirc Oxide synthase (i-NO) and (iv) vascular endothelial growth factor (VEGF)[6]. Does this classical model of acclimatisation explain all? The core physiological purpose according to the classic model that we have considered so far is centred upon the optimisation of increased delivery of O_2 to the cells through an integrated response involving increased ventilation, cardiac output and haemoglobin concentration that cumulatively serve to increase the oxygen flux across the oxygen cascade.

However authors such as Grocott[7], *et al.* have pointed out that these adaptive changes do not fully explain the observed inter individual differences in their levels of tolerance to hypobaric hypoxia. Neither the baseline Cardio-respiratory performance (VO_2 max) nor changes in the response to chronic hypoxia seem to account for inter-individual difference/s in acclimatisation[8] or performance at altitude[9]. Calbet[10], *et al.* raise a troubling question: why does VO_2 max still stay reduced after acclimatisation and normalisation of arterial oxygen content? In fact maximal oxygen consumption and stroke volume all remain reduced despite acclimatisation induced normalisation of blood oxygen content to sea-level values[11]. Cerriteli[12], has observed that pure oxygen breathing by acclimatised individual with resultant oxygen content greater than at sea-level did not normalise the VO_2 max to sea level values.

These dissonant findings signal that oxygen carriage and delivery is not the predominant factor accounting for maximal oxygen consumption at altitude. An alternative model suggested by work of Hochachka[13], *et al.*, and reflected upon by Grocott[7], *et al.* re-purposes the underlying assumption away from the preponderance of increased oxygen flux and delivery towards a decrease in oxygen demand and utilisation at the cellular level through hibernation, stunning, pre-conditioning pathways or an enhanced efficiency of metabolic substrate use[7]. In fact, hypoxia tolerant species and biological systems rarely activate the anaerobic metabolism, they rather adapt to hypoxia by reducing oxygen demand (hibernation) rather than by increasing the oxygen supply[13].

7. FAILURE OF ADAPTATION AND HIGH ALTITUDE ILLNESS

Acute high altitude illness (AHAI) is an aggregate of two syndromes: cerebral and pulmonary that can afflict un-acclimatised climbers/trekkers ascending rapidly to high altitude (defined as >2,500 m) while the cerebral syndromes encompass- Acute mountain sickness (AMS) and high altitude cerebral oedema (HACO), the pulmonary syndrome typically refers to high altitude pulmonary oedema (HAPO).

8. EPIDEMIOLOGY AND RISK

While the incidence of AMS among trekkers to the Everest base camp was around 50 per cent in those climbing to altitudes >4000 m in 5 days[14], it was nearly 84 per cent in those flying directly to 3740 m[15]. The incidence of HAPO and HACO is reported to range between 1 per cent - 4.0 per cent[14]. The risk of developing AHAI is a function of 3 inter-active factors (i) rate of ascent, (ii) the altitude reached (sleeping altitude) and (iii) individual susceptibility[14]. Other significant risk factors include a past history of high altitude illness, exertion and infection. Individuals with a past history of HAPE who ascend rapidly above 4,500 have a 60 per cent chance of recurrence[15]. It is also reported that a previous history of HAPE could be predictive of its recurrence[16], rapid ascent profiles greater than 500 m a day above 3000 m create a risk for AHAI, as also to those who ascend rapidly to altitudes >3,500 m in a day (e.g. Air travel)[17]. Maximum altitude gained too influences the likelihood of AHAI- AMS typically develops at altitudes>2,500, HAPO at > 3000 m and HACO between 4000 m - 5000 m[18]. A large body of evidence points towards individual susceptibility as an interactive outcome between: genetic and environmental factors[18,19]. Studies on Tibetan and Andean populations have revealed different genetic phenotypes[20]. Increased nitrogen oxides in the acclimatisation of both highlanders and lowlanders has been revealed, with Tibetans displaying significantly higher plasma concentrations of nitric oxide[21,22]. An underlying genetic susceptibility of AHAI has also been associated with impaired NO synthesis arising from certain NO synthase polymorphisms.

While studies on Japanese population have revealed correlations between polymorphisms of NO synthase gene with resultant lower NO synthesis and increased HAPO susceptibility, in a study on Caucasians, no such correlations could be discerned[23,24].

Likewise for the ACE gene polymorphisms, while homozygosity for the insertion variant of ACE gene, associated with lower ACE levels seems to confer performance advantage at high altitude[25,26] the association between ACE polymorphisms with high altitude illness is more complicated. While lowlander Japanese cohort showed no correlations between insertion/deletion ACE gene variants and the HAPE-susceptible and HAPE-resistant cohorts[27], research on high lander Kyrgyz cohorts have signaled an association between ACE gene insertion (I) allele and the risk of high latitude pulmonary hypertension[26,27]. Grocott[7], *et al.* attempt to reconcile these contrasting effects of ACE & NO synthase gene alleles by suggesting the possibility of this variation being an outcome of interaction between several other gene systems[28].

Genetic and epigenetic variation genes coding for hypoxia inducible factors (HIF), transcription factors that modify genetic expression in response to cellular hypoxia may also account for the individual variation to AHA susceptibility[20].

Some work points to correlation between pulmonary circulation responsiveness to hypoxia and vulnerability to HAPO. While raised pulmonary artery pressures and pulmonary vascular hyper-responsiveness to hypoxia during exercise at sea level correlates with a higher risk of HAPO on ascent to altitudes[23]. Tibetans tend to have hypo-responsive pulmonary vasculature to hypoxia compared with lowlanders[24].

9. CLINICAL PRESENTATION

AMS symptoms classically emerge between 6 h - 12 h after arrival at high altitude, often clearing up within 24 h - 72 h of stay at the same altitude. The core symptom of AMS is headache along with any of the following associated symptoms anorexia, nausea, vomiting, fatigue, dizziness and insomnia. There are no clinical signs of AMS and diagnosis is made exclusively by the symptom history within the context of recent altitude gain. Being undifferentiated, the symptom profile of AMS overlaps with several other common disorders such as dehydration, exhaustion, viral illness, hypothermia, hypoglycaemia, migraine and alcohol hangover. AMS can be better objectivised by the Lake Louise scoring system[28].

Using this system AMS is diagnosed with a score totalling to 3 or more in the presence of headache and recent ascent to high altitude by an un-acclimatised person.

HACE, which is mostly preceded by AMS, is viewed as an end stage of AMS. Clinically HACE is characterised by the emergence of: (i) altered mental state and (ii) ataxia. In a person with AMS, the presence of either altered mentation or ataxia allows for a diagnosis of HACE to be made. Absence of AMS, however, requires the presence of both altered mentation and ataxia for the diagnosis of HACE[28].

In field conditions ataxia is best screened by asking the person to walk on heel to toe tandem along a 5 m long straight line. Focal neurological signs such as hemi or paraparesis are extremely uncommon in HACE and their presence usually signifies another pathophysiology like cortical vein thrombosis or an arterial stroke. Left untreated HACE rapidly progresses to coma, coning and death within 24 h.

Table 1. AMS and HACE

System	Severity & Score
Headache	None(0)/Mild (1)/ Moderate (3)/ Severe (3)
Gastro- intestinal	None(0)/Mild (1)/ Moderate (3)/ Severe (3)
Fatigue	None(0)/Mild (1)/ Moderate (3)/ Severe (3)
Dizziness /light headedness	None(0)/Mild (1)/ Moderate (3)/ Severe (3)
Insomnia	None(0)/not as well as usual (1)/poor sleep (2) /unable to sleep (3)

10. PATHOPHYSIOLOGY

The pathophysiology of AMS and HACE is still unclear. Hackett and Roach have modelled AMS & HACE around

hypoxaemia triggered increased cerebral blood flow, volume and enhanced permeability of blood brain barrier leading to diffuse cerebral edema[7,28].

Table 2. Prevention and treatment of AMS and HACE

Prevention	Treatment
• Appropriate ascent profile (300-500 m of sleeping alt gain/day, rest day every 3rd day) • Acetazolamide (125 mg) BD, started 1-day pre and continued 3 days post ascent. Only for High-risk persons/or for unavoidable rapid ascents to 3000 m or more.	• Descent (Definitive treatment) • O_2 Supplementation • Acetazolamide (250mg) BD • Dexamethasone : 8 mg stat, 4 mg every 6 h (First –line drug for HACE, and used in severe AMS) • Portable hyperbaric chambers only when descent is not feasible.

11. HAPE

11.1 Clinical Presentation

HAPE typically occurs in the initial 2-5 days of arrival at altitudes >2,500 m, and unlike HACE, is not always preceded by AMS. It typically strikes on the second night and is rare after 5 day of continued stay at the same altitude.

The first symptoms of HAPE are the onset of severe fatigue and effort intolerance that is soon followed by dyspnea-on-exertion. Cough that is dry at onset and expectorant with pink frothy sputum later is also very common accompaniment. Only 50 per cent of HAPE patients have concurrent AMS and 14 Per cent have concurrent HACE[18], while 5 Per cent of autopsies of fatal HAPE have evidence of cerebral oedema[28].

Table 3. Prevention and treatment of AMS and HACE

Symptom	Sign
Decreased exercise tolerance	Tachypnea
Dyspnea at rest	Tachycardia
Cough	Crepts or wheeze on auscultation
Chest tightness	Central cyanosis

11.2 Sub – Clinical HAPE

Its existence was first suggested by Cremona[29], *et al.* who found that 77 per cent of climbers on Monte Rosa (4559m) had evidence of increased closing volumes, suggestive of pulmonary extravascular fluid accumulation. It is unclear, if this condition is predictive for clinical HAPE. Reviews have also reported increased pulmonary artery pressures and extravascular fluid flux during exercise at sea level, as also contribution of hypoxia to its development. However, their predictive power for high altitude HAPE is unknown as yet[30].

12. PATHOPHYSIOLOGY

HAPE is a non-cardiogenic pulmonary oedema marked by pulmonary artery hypertension possibly associated with uneven hypoxic vaso-constriction of the pulmonary micro vasculature leading to vascular leakage of fluid through over

Table 4. Diagnosis of HAPE requires at least 2 symptom and 2 sign

Prevention	Treatment
Slow ascent (not > 300 m of sleeping alt gain/day, rest every 3rd day or after 1000 m of ascent)	Rapid descent (definitive treatment (1000 m or >)
Minimise high intensity exercise soon after ascent, good insulation	Supplemental O_2 2-4 L/Mt titrated to keep Sa O_2 at 90%
In HAPO- Susceptible: Nifedipine (sustained release) 20 mg BD or tds, started 1-day pre-ascent, continued for 5 day post .	Nifedipine (Sustained release) 20 mg tds. Portable hyperbaric chambers only if immediate descent not possible

perfusion, stress failure of alveolar capillary interfaces, or both. Individual susceptibility to HAPE is often associated with an exaggerated increase in pulmonary artery pressures as a response to the stress challenge of hypoxia and exercise[31,32]. The exact basis for exaggerated hypoxic pulmonary vasoconstriction remains undefined, although the model of HAPE pathophysiology proposed by Hultgren[31], *et al.* suggests a primary role of (i) blunted Hypoxic ventilator response (HVR), (ii) hyperactive hypoxic pulmonary vasoconstrictive response, and (iii) Genetic vulnerability, acting in conjunction with four secondary variables (i) sympathetic arousal, (ii) endothelial dysfunction, (iii) Cold and (iv) exercise to generate increased pulmonary artery pressure, which then triggers increased capillary pressures, endothelial stress and fluid leakage across the alveolar capillary interfaces. Decreased removal of sodium and water from the alveoli further compounds the problem of excessive fluid accumulation.

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